Original Article

The expression of tumor necrosis factor receptor 2 is correlated with the prognosis of cancer: a systematic review and meta-analysis

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Contributions: (I) Conception and design: Both authors; (II) Administrative support: Both authors; (III) Provision of study materials or patients: Both authors; (IV) Collection and assembly of data: Both authors; (V) Data analysis and interpretation: Both authors; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

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Background: Tumor necrosis factor receptor 2 (TNFR2) is a subtype of the tumor necrosis factor receptors and is known to promote cancer progression by enhancing cancer cell proliferation and inducing immune suppression. More recently, there are reports that TNFR2 expression is related to the prognosis of patients with cancer, including lung, breast, esophageal, colorectal cancer, and lymphoma. In this study, the correlation between the expression of TNFR2 and the prognosis and clinicopathological factors of cancer was systematically evaluated. This study aimed at elucidating the relationship between TNFR2 and prognosis in patients with cancer.

Methods: PubMed, Embase, and Cochrane Library were searched and a meta-analysis was performed to assess the prognostic and clinicopathological values of TNFR2 expression in patients with cancer.

Results: Nine studies with 2,229 patients were included. High expression of TNFR2 was significantly correlated with poor overall survival (OS) [hazard ratio (HR), 1.76; 95% confidence interval (CI): 1.37–2.27; P<0.001] and disease-free survival (DFS) (HR, 2.75; 95% CI: 1.92–3.92; P<0.001). High expression of TNFR2 was also significantly associated with higher tumor grade [odds ratio (OR), 1.58; 95% CI: 1.26–1.98; P<0.001], higher tumor stage (OR, 2.41; 95% CI: 1.62–3.60; P<0.001) and higher clinical stage (OR, 1.80; 95% CI: 1.44–2.23; P<0.001).

Conclusions: High expression of TNFR2 was related to poor prognosis and could be a prognostic factor in patients with cancer.

Keywords: Cancer; meta-analysis; prognosis; tumor necrosis factor receptor 2 (TNFR2)

Submitted Feb 21, 2024. Accepted for publication Jun 30, 2024. Published online Aug 06, 2024.
doi: 10.21037/tcr-24-275
View this article at: https://dx.doi.org/10.21037/tcr-24-275

Introduction

The most immediate task after a diagnosis of cancer is to determine the prognosis and treatment for the patients (1). The decision of prognosis is made in consideration of various clinicopathological and prognostic factors (1). With the recent development of technology, the discovery of biomarkers that can determine the prognosis of cancer is active (2).

Tumor necrosis factor receptor 2 (TNFR2) is a component of the tumor necrosis factor receptors and is involved in diverse signal pathways on the interaction with tumor necrosis factor (3,4). The signaling process of the TNFR2 pathway is not well understood (4). TNFR2 is expressed myeloid-derived suppressor cells, endothelial cells, T lymphocytes, myocardial cells, oligodendrocytes, and thymocytes (4). TNFR2 is known to play an important role in inflammatory process and immune regulation (4). Moreover, the role of TNFR2 in cancer progression has recently come to reveal (5). TNFR2 promotes the progression of cancer by upregulating the proliferation of cancer cell and inducing immune suppression and escape (4). Furthermore, reports that TNFR2 expression is related to poor prognosis are being released in various cancers, including lung, breast, esophageal, colorectal cancer, and lymphoma (3,4,6-12). However, there is no systematic review of the correlation between TNFR2 expression and the prognosis of patients with cancer.

Thus, we conducted a systematic review and meta-analysis to explore the prognostic and clinicopathological values of TNFR2 expression in patients with cancer. We present this article in accordance with the PRISMA reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-275/rc).

Methods

Search strategy

PubMed, Embase, and Cochrane Library were searched. The search was performed until July 2023 using the following keywords: (TNFR2 or tumor necrosis factor receptor 2) and (cancer or carcinoma or malignancy) and (prognosis or survival or outcome). A manual search was also carried out.

Inclusion and exclusion criteria

Inclusion criteria were as follows: (I) the correlation of TNFR2 expression with prognosis was presented in human cancer; (II) survival data were provided for calculating hazard ratio (HR) and 95% confidence interval (CI). The article presented with conference abstracts, review, inaccurate data, and non-English articles were excluded.

Data extraction and quality assessment

Two authors reviewed the included studies and collected basic information independently. When there was a difference in the information collected, an agreement was reached through discussion.

Two authors also assessed the quality of the enrolled studies using the Newcastle-Ottawa Scale individually. If there were any differences in the results, a consensus was reached.

Statistical analysis

A meta-analysis using StataSE12 (Stata, College Station, TX, USA) was performed. I^2 statics was applied to determine the degree of heterogeneity among the enrolled studies. The pooled HR and odds ratio (OR) with 95% CI were calculated for assessing the prognostic and clinicopathological values of TNFR2 expression. We also performed funnel and filled plots with Egger test to reveal the publication bias. And the sensitivity analysis was performed to check the effect of individual studies. It was judged to be statistically significant only when the P value was less than 0.05.

Results

Basic information of the included studies

Nine eligible studies were selected through the literature search and review (*Figure 1*). The basic information of included studies is given in *Table 1*. The enrolled studies were comprised of 2,229 patients with cancer, including non-small cell lung cancer (n=2), esophageal squamous cell carcinoma (n=2), breast cancer (n=1), colorectal cancer (n=1), and lymphoma (n=3).

Highlight box

Key findings
- High expression of tumor necrosis factor receptor 2 (TNFR2) was related to poor prognosis.

What is known and what is new?
- High expression of TNFR2 was related to poor survival.
- High expression of TNFR2 was significantly correlated with poor overall survival and disease-free survival.

What is the implication, and what should change now?
- High expression of TNFR2 was also significantly associated with higher tumor grade, higher tumor stage, and higher clinical stage.

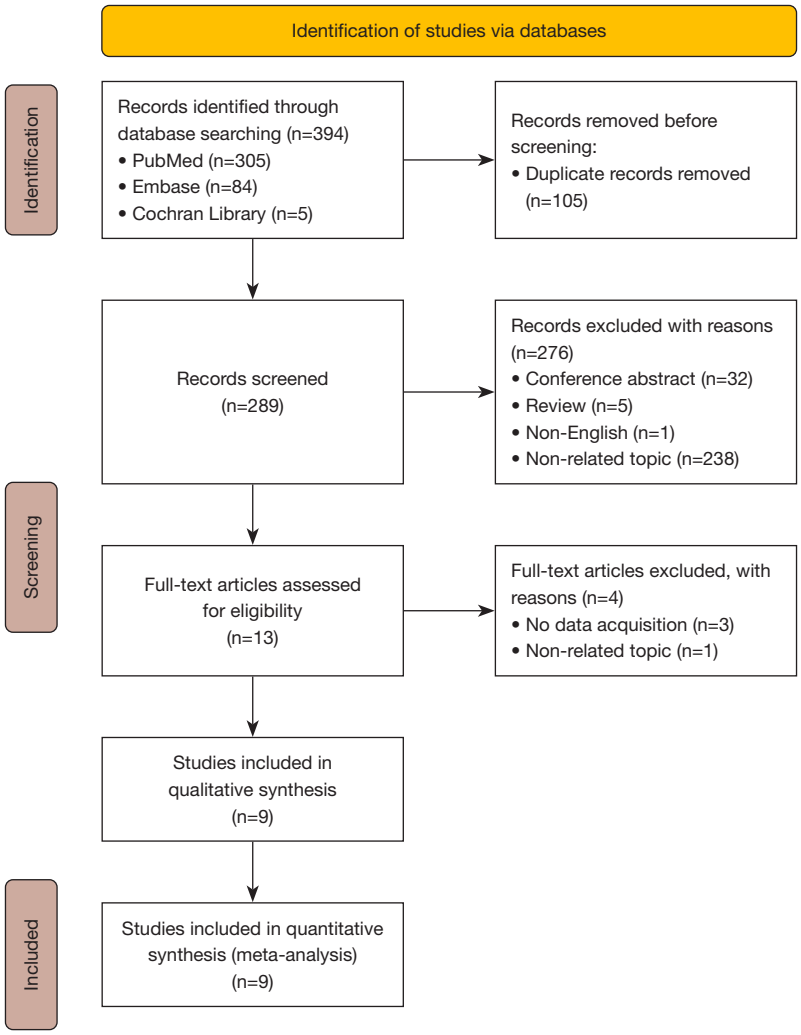


Figure 1 Flow diagram of study selection.

Correlation between TNFR2 expression and overall survival (OS)

The pooled HR was calculated using random effects model (I^2=57.8%; P=0.02). The pooled HR for nine studies was 1.76 (95% CI: 1.37–2.27; P<0.001), indicating that high expression of TNFR2 was correlated with poor OS in patients with cancer (*Figure 2A*). We also performed subgroup analyses according to cancer type (solid cancer *vs.* lymphoma) and TNFR2 detected sample (tissue *vs.* serum). The analyses revealed that all groups maintained significant results (HR, 1.50; 95% CI: 1.21–1.87; P<0.001 for solid cancer; HR, 2.95; 95% CI: 1.85–4.69; P<0.001 for lymphoma; HR, 1.72; 95% CI: 1.41–2.11; P<0.001 for tissue; HR, 1.88; 95% CI: 1.19–2.98; P=0.007 for serum) (*Table 2*, *Figure 2B*,*2C*).

Correlation between TNFR2 expression and disease-free survival (DFS)

The pooled HR was calculated using fixed effects model (I^2=0.0%; P=0.86). The pooled HR for five studies was 2.75 (95% CI: 1.92–3.92; P<0.001), implying that high expression of TNFR2 was correlated with poor DFS in patients with cancer (*Figure 3A*). Progression-free survival and event-free survival were considered as DFS in this analysis. There were only five studies reporting the correlation between DFS and TNFR2, so five studies were

Table 1 The basic information of included studies

Study	Country	Cancer type	Sample size	Sex (male/female)	Age (years)	Study period	Follow-up (months)	Clinical outcome	TNFR2 detection	Cut-off value of TNFR2 expression	Survival analysis	NOS
Zhang *et al.*, 2019, (4)	China	Non-small cell lung cancer	71	41/30	NA	2006–2010	NA	OS, DFS	Tissue (IHC)	≥ score 4 (the product of the proportion and intensity scores)	MVA	7
Liu *et al.*, 2018, (11)	China	Esophageal squamous cell carcinoma	589	455/134	NA	2008–2014	NA	OS	Tissue (IHC)	> score 4 (the product of the proportion and intensity scores)	SC	6
Yang *et al.*, 2018, (6)	China	Esophageal squamous cell carcinoma	431	245/186	NA	2008–2014	December 2016	OS	Tissue (IHC)	> score 4 (the product of the proportion and intensity scores)	SC	7
Yang *et al.*, 2017, (3)	China	Breast cancer (ductal invasive, others)	125	–	NA	2005–2010	December 2015	OS, DFS	Tissue (IHC)	≥ score 4 (the product of the proportion and intensity scores)	MVA	8
Babic *et al.*, 2016, (7)	USA	Colorectal cancer	544	225/319	NA	1990–2010	Median 138 (range, 46.8–246)	OS, CSS	Serum	3,186–9,572 pg/mL	MVA	9
Nakamura *et al.*, 2013, (12)	Japan	Diffuse large B-cell lymphoma	154	87/67	NA	2002–2008	NA	OS, PFS	Serum	≥20 ng/mL	MVA	7
Heemann *et al.*, 2012, (10)	Sweden	T-cell non-Hodgkin lymphoma	117	69/48	Median 58 (range, 18–78)	1993–2007	NA	OS, EFS	Serum	≥2.16 ng/mL	MVA	7
Gregorc *et al.*, 2007, (9)	Italy	Non-small cell lung cancer	88	NA	Mean 62.5 (range, 21–80)	NA	Median 44.3	OS	Serum	>1 ng/mL	MVA	8
Goto *et al.*, 2006, (8)	Japan	Non-Hodgkin lymphoma	110	68/42	NA	1997–2002	November 2003	OS, EFS	Serum	>15 ng/mL	MVA	8

TNFR2, tissue necrosis factor receptor 2; NOS, Newcastle-Ottawa Scale; NA, not available; OS, overall survival; DFS, disease-free survival; IHC, immunohistochemistry; MVA, multivariate analysis; SC, survival curve; CSS, cancer-specific survival; PFS, progression-free survival; EFS, event-free survival.

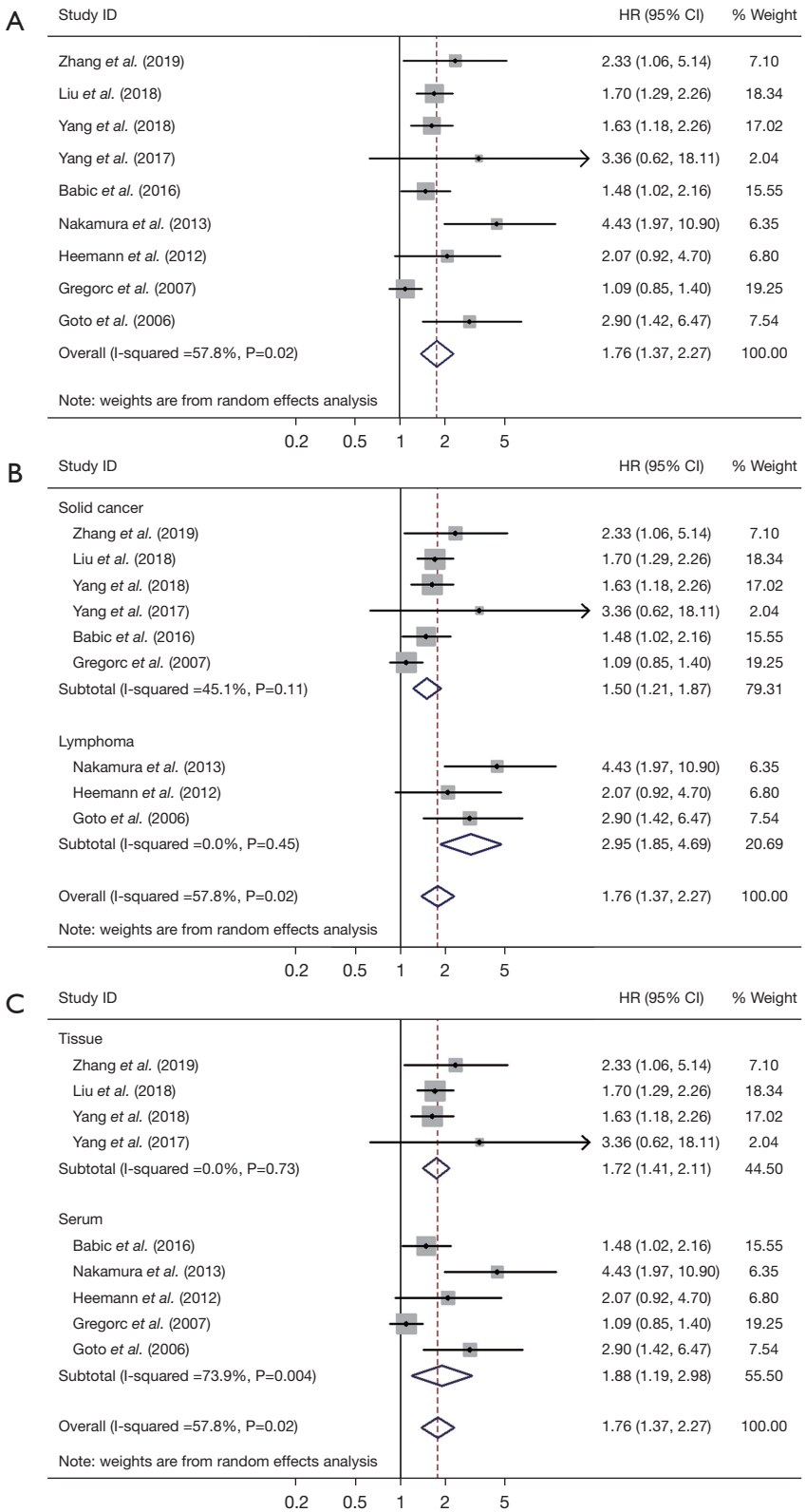


Figure 2 Forest plot for the correlation between TNFR2 expression and OS (A), stratified by cancer type (B), and TNFR2 detected sample (C). HR, hazard ratio; CI, confidence interval; TNFR2, tumor necrosis factor receptor 2; OS, overall survival.

Table 2 Subgroup analysis of the correlation between TNFR2 expression and OS in patients with cancer

Subgroup	Number of studies	Number of patients	Pooled HR (95% CI)	P value	Heterogeneity	
					I^2 (%)	P value
Cancer type						
Solid cancer	6	1,848	1.50 (1.21–1.87)	<0.001	45.1	0.11
Lymphoma	3	381	2.95 (1.85–4.69)	<0.001	0.0	0.45
TNFR2 detected sample						
Tissue	4	1,216	1.72 (1.41–2.11)	<0.001	0.0	0.73
Serum	5	1,013	1.88 (1.19–2.98)	0.007	73.9	0.004

TNFR2, tissue necrosis factor receptor 2; OS, overall survival; HR, hazard ratio; CI, confidence interval.

analyzed. In subgroup analyses according to cancer type (solid cancer *vs.* lymphoma) and TNFR2 detected sample (tissue *vs.* serum), all groups showed significant results (HR, 3.43; 95% CI: 1.77–6.64; P<0.001 for solid cancer and tissue; HR, 2.51; 95% CI: 1.64–3.83; P<0.001 for lymphoma and serum) (*Table 3*, *Figure 3B,3C*).

Correlation between TNFR2 expression and clinicopathological factors in solid cancer

High expression of TNFR2 was significantly correlated with higher tumor grade (OR, 1.58; 95% CI: 1.26–1.98; P<0.001), higher tumor stage (OR, 2.41; 95% CI: 1.62–3.60; P<0.001) and higher clinical stage (OR, 1.80; 95% CI: 1.44–2.23; P<0.001), but not with age, gender, tumor size and lymph node metastasis (*Table 4*, *Figure 4A-4C*).

Publication bias

The funnel plot for OS looked asymmetrical. Indeed, Egger test proved a small-study effect (P=0.02). However, the pooled HR was still significant in the filled funnel plot (HR, 1.47; 95% CI: 1.13–1.91; P=0.004) (*Figure 5A,5B*).

The funnel plot for DFS did not show publication bias (Egger test; P=0.19). The filled test revealed that initial data was unchanged (HR, 2.75; 95% CI: 1.92–3.92; P<0.001) (*Figure 5C,5D*).

Sensitivity analysis

The sensitivity analyses demonstrated that the initial results were reliable and consistent even excluding the effects of individual studies (HR, 1.54; 95% CI: 1.34–1.77 for OS; HR, 2.75; 95% CI: 1.92–3.92 for DFS) (*Figure 6A,6B*).

Discussion

TNFR2 is a transmembrane protein consisting of an extracellular domain with four complementarity determining regions (5). TNFR2 is known to play distinct roles in cancer progression and metastasis (5). Some researchers have reported that TNFR2 participates in enhancing TNF-induced or vascular endothelial growth factor-related cancer cell proliferation and TNFR2 promotes cancer progression and metastasis by inducing an immunosuppressive microenvironment (5).

More recently, the prognostic role of TNFR2 expression in cancer has been revealed. Considering the results of the studies in cancer tissue, Liu *et al.* and Yang *et al.* demonstrated that high expression of TNFR2 is correlated with poor OS in patients with esophageal squamous cell carcinoma (6,11). Zhang *et al.* demonstrated that high expression of TNFR2 is correlated with shorter OS and DFS in patients with non-small cell lung cancer (4). Yang *et al.* reported that TNFR2 expression is shown to significantly impact the DFS of patients with breast cancer (3). With respect to serum, Babic *et al.* revealed that higher TNFR2 levels are correlated with a significant increase in overall mortality of patients with colorectal cancer (7). Nakamura *et al.*, Heemann *et al.*, and Goto *et al.* showed that high level of serum TNFR2 is related to disease progression and shorter OS in patients with lymphoma (8,10,12).

Here, a meta-analysis was conducted for a systematic understanding of the correlation between TNFR2 expression and survival in patients with cancer.

In this study, we demonstrated that high expression of TNFR2 was correlated with poor OS and DFS in patients with cancer. In addition, we revealed that the significant association was maintained regardless of cancer type

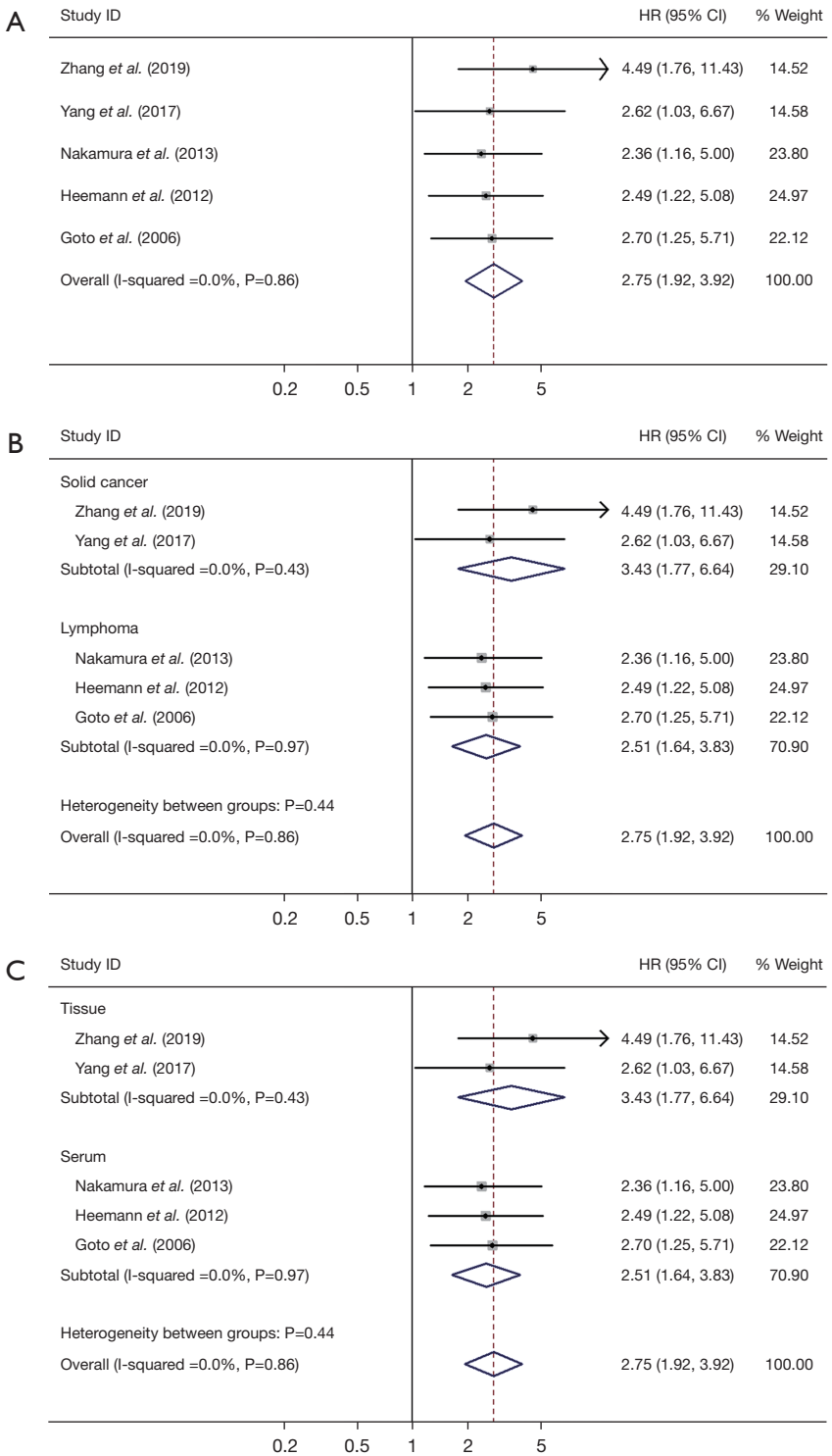


Figure 3 Forest plot for the correlation between TNFR2 expression and DFS (A), stratified by cancer type (B), and TNFR2 detected sample (C). HR, hazard ratio; CI, confidence interval; TNFR2, tumor necrosis factor receptor 2; DFS, disease-free survival.

Table 3 Subgroup analysis of the correlation between TNFR2 expression and DFS in patients with cancer

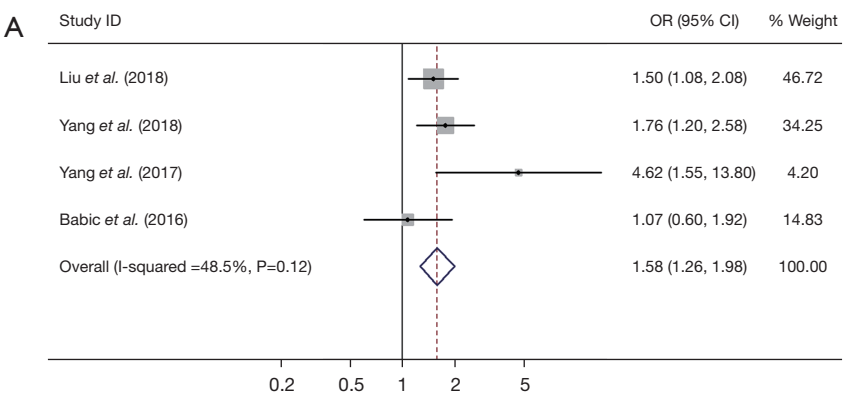
Subgroup	Number of studies	Number of patients	Pooled HR (95% CI)	P value	Heterogeneity	
					I^2 (%)	P value
Cancer type						
Solid cancer	2	196	3.43 (1.77–6.64)	<0.001	0.0	0.43
Lymphoma	3	381	2.51 (1.64–3.83)	<0.001	0.0	0.97
TNFR2 detected sample						
Tissue	2	196	3.43 (1.77–6.64)	<0.001	0.0	0.43
Serum	3	381	2.51 (1.64–3.83)	<0.001	0.0	0.97

TNFR2, tissue necrosis factor receptor 2; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval.

Table 4 The correlation between TNFR2 expression and clinicopathological factors in solid cancer

Factors	Number of studies	Number of patients	Pooled OR (95% CI)	P value	Heterogeneity		
					I^2 (%)	P value	Model
Age (old *vs.* young)	4	1,216	1.07 (0.85–1.35)	0.57	0.0	0.81	Fixed
Sex (male *vs.* female)	4	1,635	1.05 (0.84–1.30)	0.68	0.0	0.84	Fixed
Tumor size (large *vs.* small)	3	785	1.30 (0.38–4.39)	0.68	76.0	0.02	Random
Tumor grade (high *vs.* low)	4	1,689	1.58 (1.26–1.98)	<0.001	48.5	0.12	Fixed
Tumor stage (high *vs.* low)	2	556	2.41 (1.62–3.60)	<0.001	30.0	0.23	Fixed
Lymph node metastasis (present *vs.* absent)	4	1,216	1.14 (0.74–1.76)	0.55	63.2	0.043	Random
Clinical stage (high *vs.* low)	5	1,760	1.80 (1.44–2.23)	<0.001	16.7	0.31	Fixed

TNFR2, tissue necrosis factor receptor 2; OR, odds ratio; CI, confidence interval.



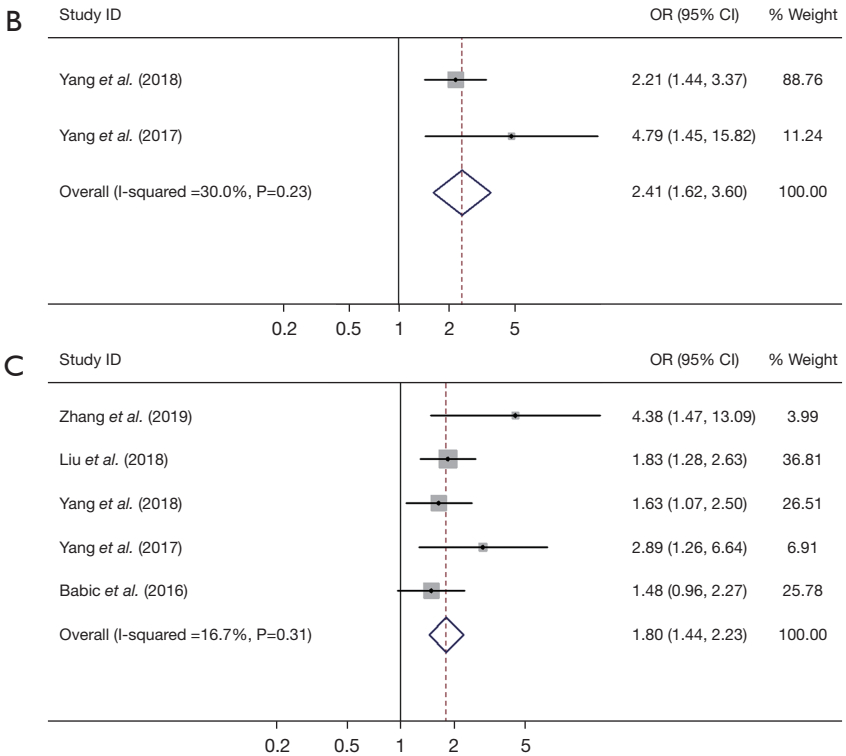


Figure 4 Forest plot for evaluating the correlation between TNFR2 expression and tumor grade (A), tumor stage (B) and clinical stage (C) in solid cancer. OR, odds ratio; CI, confidence interval; TNFR2, tumor necrosis factor receptor 2.

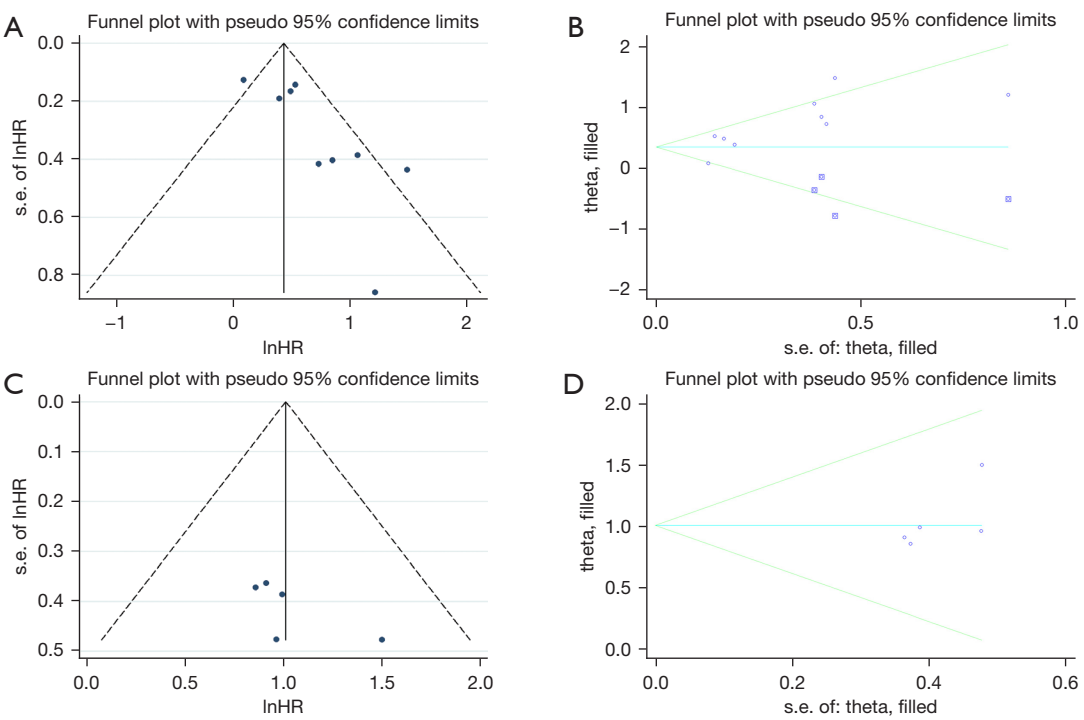


Figure 5 Funnel plot and fill method for the correlation between TNFR2 expression and OS (A,B), and DFS (C,D). HR, hazard ratio; s.e., standard error; TNFR2, tumor necrosis factor receptor 2; OS, overall survival; DFS, disease-free survival.

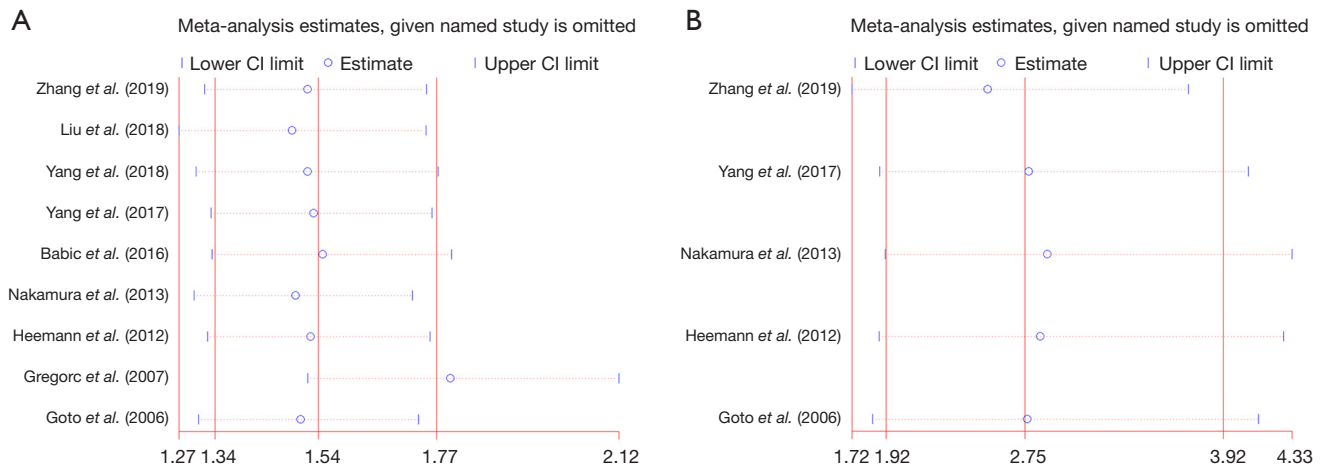


Figure 6 Sensitivity analysis for the correlation between TNFR2 expression and OS (A), and DFS (B). CI, confidence interval; TNFR2, tumor necrosis factor receptor 2; OS, overall survival; DFS, disease-free survival.

(solid cancer *vs.* lymphoma) and TNFR2 detected sample (tissue *vs.* serum). We also identified that high expression of TNFR2 was significantly correlated with higher tumor grade, tumor stage, and clinical stage in solid cancer.

For the first time, we systematically examined the correlation between TNFR2 expression and the prognosis in patients with cancer. However, this study has some limitations. Firstly, the number of included studies and sample size were limited. Secondly, several HR was calculated from the survival curve, which might cause a slight error. Lastly, the articles studied through serum might have influenced our results because the cut-off value of TNFR2 expression varies.

Conclusions

In summary, high expression of TNFR2 was related to poor prognosis and could be a prognostic factor in patients with cancer.

Acknowledgments

Funding: This work was supported by the 2024 education, research, and student guidance grant funded by Jeju National University.

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-275/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-275/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-275/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Nicolini A, Ferrari P, Duffy MJ. Prognostic and predictive

biomarkers in breast cancer: Past, present and future. Semin Cancer Biol 2018;52:56-73.
2. Nair M, Sandhu SS, Sharma AK. Prognostic and Predictive Biomarkers in Cancer. Curr Cancer Drug Targets 2014;14:477-504.
3. Yang F, Zhao Z, Zhao N. Clinical implications of tumor necrosis factor receptor 2 in breast cancer. Oncol Lett 2017;14:2393-8.
4. Zhang YW, Chen QQ, Cao J, et al. Expression of tumor necrosis factor receptor 2 in human non-small cell lung cancer and its role as a potential prognostic biomarker. Thorac Cancer 2019;10:437-44.
5. Ham B, Fernandez MC, D'Costa Z, et al. The diverse roles of the TNF axis in cancer progression and metastasis. Trends Cancer Res 2016;11:1-27.
6. Yang D, Li R, Wang H, et al. Clinical significance of tumor necrosis factor receptor 2 in middle and lower thoracic esophageal squamous cell carcinoma. Oncol Lett 2018;16:2971-8.
7. Babic A, Shah SM, Song M, et al. Soluble tumour necrosis factor receptor type II and survival in colorectal cancer. Br J Cancer 2016;114:995-1002.
8. Goto N, Tsurumi H, Takemura M, et al. Serum-soluble tumor necrosis factor receptor 2 (sTNF-R2) level determines clinical outcome in patients with aggressive non-Hodgkin's lymphoma. Eur J Haematol 2006;77:217-25.
9. Gregorc V, Spreafico A, Floriani I, et al. Prognostic value of circulating chromogranin A and soluble tumor necrosis factor receptors in advanced nonsmall cell lung cancer. Cancer 2007;110:845-53.
10. Heemann C, Kreuz M, Stoller I, et al. Circulating levels of TNF receptor II are prognostic for patients with peripheral T-cell non-Hodgkin lymphoma. Clin Cancer Res 2012;18:3637-47.
11. Liu Z, Ma C, Ma G, et al. High expression of tumor necrosis factor receptor 2 in tissue is associated with progression and prognosis of esophageal squamous cell carcinoma. Hum Pathol 2018;80:179-85.
12. Nakamura N, Goto N, Tsurumi H, et al. Serum level of soluble tumor necrosis factor receptor 2 is associated with the outcome of patients with diffuse large B-cell lymphoma treated with the R-CHOP regimen. Eur J Haematol 2013;91:322-31.

Cite this article as: Koh HM, Han N. The expression of tumor necrosis factor receptor 2 is correlated with the prognosis of cancer: a systematic review and meta-analysis. Transl Cancer Res 2024;13(8):4231-4241. doi: 10.21037/tcr-24-275

